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Imbalance and dysfunction of transient receptor potential channels contribute to the pathogenesis of hypertension

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Intracellular Ca^{2+} homeostasis is essential for vascular function and blood pressure regulation. Because of their unique roles in regulating intracellular Ca^{2+} concentration and vascular function, a novel class of non-selective cation channels, called transient receptor potential (TRP) channels, have emerged at the frontier of hypertension research. Based on their role in vasculature function regulation, TRP channels can be divided into two functional subtypes: one that participates in vasoconstriction and one that participates in vasodilatation. A functional imbalance of these two subtypes of TRP channels may disturb intracellular calcium ($[Ca^{2+}]i$) homeostasis, and the consequent vascular dysfunction may contribute to the development of hypertension. The potential of these TRP channels as novel pharmacological targets for the treatment of human hypertension is of great interest.

TRP channels, Ca^{2+} homeostasis, vascular function, hypertension

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Hypertension is a principal risk factor for atherosclerosis, stroke, myocardial infarction, heart failure, and end-stage renal failure and is emerging as an important global public-health challenge [1]. The pathogenesis of hypertension involves genetic and environmental factors. Several pathways are thought to elevate blood pressure, including increased sympathetic nerve activity, activation of the renin-angiotensin system, endothelial lesions, abnormal renal sodium handling, and vascular dysfunction [2]. Importantly, intracellular Ca^{2+} homeostasis is essential for vascular function and blood pressure regulation as well as hormone secretion. Disturbance of intracellular Ca^{2+} homeostasis has been reported in both experimental and human hypertension [3,4].

Two sources are available to elevate the intracellular Ca^{2+} concentration ($[Ca^{2+}]i$). In one process, the inositol-1,4,5-triphosphate (IP_3) receptor mediates Ca^{2+} release from the internal Ca^{2+} stores of the endoplasmic reticulum (ER). Store-operated Ca^{2+} channels (SOCs, or capacitative Ca^{2+} entry channels) are activated through IP_3-induced Ca^{2+} release and consequently deplete Ca^{2+} from ER stores [5]. ER and sarcoplasmic reticulum (SR) stores are released through the stimulation of G-protein-coupled receptors, which activate phospholipase C, consequently generating IP_3 and activating the diacylglycerol (DAG) signal pathways. TRPCs (TRPC1-7), TRPC2, TRPC3, TRPC6 and TRPC7 have been reported to be activated by DAG [6–8]. Numaga et al. [9] established TRPC3 as a DAG-activated cation channel (DACCs) in B-cells. DAG-activated TRPC6 signals the membrane translocation and activation of PKC and thereby induces RhoA activation and endothelial contraction [10].

Another Ca^{2+} source is influx from the extracellular milieu through several types of ion channels, including

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Na^+/Ca^{2+} exchanger, ligand-gated cation channels (LGCs), receptor-activated cation channels (RACs), and stretch-activated cation channels (SACs). Contractile VSMCs express Ca^{2+} transporters, including voltage-gated L-type Ca^{2+} channels (LTCCs) and sarco/endoplasmic reticulum Ca^{2+} ATPase type 2a (SERCA2a) pump, which maintain low resting cytosolic Ca^{2+} and allow dynamic changes of Ca^{2+} in the spatial and temporal domain, while non-contractile VSMCs have significantly reduced voltage dependence of Ca^{2+} entry [11]. In the past two decades, a novel family of nonselective cation channels called transient receptor potential (TRP) channels has been intensively investigated. Unlike voltage-gated ion channels, TRP channels lack a voltage-sensing moiety; they therefore function as voltage-independent, nonselective cation channels that are permeable to Na^+, K^+, Cs^+, Li^+, Ca^{2+}, and Mg^{2+} [12]. TRP channels are researched in the fields as diverse as oncology, urology, dermatology, migraine, inflammation and pain. Among the TRPC, TRPV and TRPM subfamilies as well as TRPA1 appear to be involved in glioma, breast, gut, head and neck cancers to lung and prostate cancers [13]. Streng et al. [14] showed that hydrogen sulfide-sensitive TRPA1 ion channel was expressed in rat urinary bladder. The available evidence that identifies TRPA1 and TRPV1 contribute to migraine and cluster headache trigger [15,16], and TRPA1 activity impacts on cerebral circulation and pain sensitivity [17]. TRPA1 channels are activated by ROS, reactive nitrogen species (RNS) and other electrophiles, thus identifying the channel as a sensor of oxidative and nitrative stress generated at sites of inflammation or tissue injury [18]. Because of their unique roles in regulating the intracellular Ca^{2+} concentration and vascular function, the identification of mammalian TRP channels marked a new starting point in the molecular identification of Ca^{2+} entry pathways that contribute to the development of cardiovascular disease.

1 Distribution and functions of TRP channels

The TRP channels were named after the *Drosophila melanogaster* ion channel that is mutated in the *trp* gene, as first reported by Minke [19]. Twenty-eight members of the TRP channel superfamily have been identified in almost every tissue of mammals [20]. Based on their amino acid sequence homology, mammalian TRP channels can be divided into six subfamilies, including TRP canonical (TRPC; TRPC1-7), TRP vanilloid (TRPV; TRPV1-6), TRP melastatin (TRPM; TRPM1-8), TRP mucolipin (TRPML; TRPML1-3), TRP ankyrin (TRPA; TRPA1) and TRP polycystin (TRPP; TRPP2, TRPP3, TRPP5) [20]. In general, all seven members of TRPC [21–25]; TRPV1, -2, -4 [26–28]; all TRPM, except TRPM5 [27] and TRPP1 and -2 [29,30], have been reported to expressed in vascular endothelial cells (ECs) from various sources. TRP channels other than TRPV5, TRPV6, and TRPM1 are found in arterial smooth muscle from different segments of the vasculature [31]. Based on their roles in regulating vasculature functioning, TRP channels can be divided into two functional subtypes: one that participates in vasoconstriction and one that participates in vasodilatation.

2 TRP channels participate in vasoconstriction

TRPC1 was the first cloned mammalian homologue of *Drosophila trp* [32]. Several studies have suggested that TRPC1 is a component of the store-operated Ca^{2+} entry pathway in both vascular smooth muscle cell (VSMC) and ECs. Over-expression of the human *trpc1* gene in rat pulmonary artery enhanced vasoconstriction via store depletion-mediated Ca^{2+} influx [33]. One study found that thapsigargin-stimulated store-operated current was reduced in TRPC1 siRNA- or TRPC1 antisense-expressing cells [34]. Ahmmed et al. [35] demonstrated that phosphorylation of TRPC1 via PKC alpha was an important determinant of store-operated Ca^{2+} entry in human ECs. Additionally, TRPC1 proteins confer PKC and phosphoinositol activation on native heteromeric TRPC1/C5 channels in vascular smooth muscle [36]. TRPC3 has been shown to be involved in the agonist-induced depolarization and vasoconstriction of arterial SMCs, and suppression of TRPC3 expression was found to significantly decrease the depolarization and constriction of intact cerebral arteries in response to UTP [37]. Xu et al. [38] found that sphingolipids and TRP channels are functionally linked in VSMCs and that the sphingolipids' metabolite, sphingosine-1-phosphate, activates TRPC5, thus controlling VSMC motility. TRPC6 has been suggested to have a major role in the regulation of myogenic tone [39]. The inhibition of TRPC6 has been found to decrease TRPC6 protein expression and greatly attenuate arterial smooth muscle depolarization and constriction caused by elevated pressure in intact cerebral arteries [39]. In another study, the isolated aortic rings and cerebral arteries of TRPC6-deficient mice showed an enhanced agonist-induced constriction [40]. Likewise, TRPC6-deficient mice showed a higher basal cation entry in VSMC, increased TRPC-carried cation currents, and more depolarized membrane potentials because of constitutively active TRPC3 channels [40]. These data implicate the concept of the formation of TRPC3/6 heteromeric complexes with a tightly receptor-operated TRPC6 subunit suppressing TRPC3 basal activity [41]. Furthermore, some multimerization data show that TRPC3/6 tetramers are formed in a heterologous expression system [42], in brain synaptosomes [43], and in polarized epithelial cells [44]. These findings may be compatible with the hypothesis that, in such heteromultimeric complexes, TRPC6 may suppress the basal activity of TRPC3, leading to a tightly receptor-regulated cation channel complex required for the physiological regu-

lation of smooth muscle tone [40]. Recently, the studies indicate a critical role of TRPM4 in myogenic constriction of cerebral arteries. Pressure-induced SMC depolarization was attenuated in isolated cerebral arteries treated with TRPM4 antisense oligodeoxynucleotides. Activation of TRPM4-dependent currents contributed to myogenic vasoconstriction of cerebral arteries [45]. *In vivo* suppression of TRPM4 decreases cerebral artery myogenic constrictions and impairs auto-regulation, thus implicating TRPM4 channels and myogenic constriction as major contributors to cerebral blood flow regulation in the living animal [46]. Narayanan et al. [47] demonstrated that TRPP2 was expressed in SMCs of resistance-size cerebral arteries and contributed to the myogenic response. One member of TRPV subfamily, TRPV2, was found to be expressed in mouse aortic, mesenteric and basilar arterial myocytes and could be activated by membrane stretch and hypotonic stimulation [48]. Whether TRPV2 is involved in the generation of myogenic tone remains to be elucidated.

3 TRP channels contribute to vasodilatation

Some TRP channels are present in both vascular endothelial and VSMCs, and their role in the regulation of local vascular tone can be quite different. The synthesis and release of endothelium-derived relaxing factors (EDRFs) are linked to an increase in cytosolic Ca^{2+} concentration, EDRFs produced by endothelial cells not only control vascular tone, but also have multiple beneficial effects including the modulation of platelet aggregation, the inhibition of leucocyte adhesion, and the control of VSMC proliferation [49,50]. One of the most important functions of the endothelium is to modulate vascular tone. TRPC1/TRPC3 channels were found to be present in freshly isolated VSMCs, were inhibited by the NO/cGMP/PKG pathway and contributed to NO-induced vasodilatation [51]. TRPC3 was also detected in human and rodents' vascular ECs and facilitated endothelium-derived hyperpolarization-mediated resistance artery vasodilator activity [52,53]. TRPC4 proteins have also been identified as indispensable components of store-operated Ca^{2+} channels in mouse aortic ECs, as agonist-activated Ca^{2+} entry into TRPC4-deficient ECs was found to be drastically decreased, leading to a dramatically impaired endothelium-dependent relaxation [54]. TRPV1 is abundant in the endothelium. In freshly isolated rodent mesenteric arteries, activation of TPRV1 by its agonist capsaicin elicited an acute release of NO from ECs and vasodilatation, which was inhibited by the TRPV1 antagonists and was absent from arteries of TRPV1-deficient mice [26]. TRPV4 channels in the vascular ECs and SMCs are critically involved in the vasodilatation of mesenteric arteries in response to endothelial-derived factors [28]. One study found that the genetically encoded loss-of-function of *trpv4* resulted in a loss of shear stress-induced vasodilatation, a response pattern largely dependent on endothelial TRPV4 expression [55]. In a previous study, we demonstrated that TRPM8 activation, by its agonist menthol, antagonized vasoconstriction by inhibiting Ca^{2+} signaling-mediated RhoA/ROCK activation in the vasculature [56]. TRPA1 channels are present in the endothelium and mediated vasodilatation via endothelium-dependent and independent mechanisms [57,58]. The role of TRPA1 in the cardiovascular system remains elusive (Table 1).

4 TRP channel subtype C dysfunction promotes the development of hypertension

Abnormal expression and dysfunction of TRP channels have been reported in both hypertensive patients and animal models. Alterations of cellular cation influx (e.g., Ca^{2+} or Na^{+} influx), in peripheral blood cells or VSMCs, have frequently been described in primary hypertension. The recruitment of circulating peripheral monocytes, their activation and their differentiation into tissue macrophages play an important role in the early stages of atherosclerotic lesion formation [59]. Thilo et al. [60] observed an approximately 8-fold increase of TRPC3 transcripts in monocytes from patients with essential hypertension compared to normotensive control subjects, demonstrating a significant correlation between TRPC3 transcripts and systolic blood pressure, expression of IL-1beta, and TNF-alpha. In addition, increased TRPC3 and TRPC5 expression in monocytes of patients with essential hypertension, a subsequent store-operated Ca^{2+} influx, and increased 1-oleoyl-2-acetyl-sn-glycerol-induced cation influx in monocytes of patients with essential hypertension were observed [61]. Liu et al. [1] compared the expression level and function of TRPCs between essential hypertensive patients and normotensive control subjects. They demonstrated increased TRPC3 and TRPC5 protein expression and an increase in the gadolinium/calcium-influx ratio via TRPCs in monocytes of patients with essential hypertension [1]. Furthermore, they demonstrated an increase in TRPC3 expression in VSMCs and aortic tissues and TRPC3-related Ca^{2+} influx in VSMCs from spontaneously hypertensive rats (SHRs), which was associated with enhanced contraction in vasculature from SHRs compared with the normotensive WKY rats [4]. Thus, increased TRPC3 channel protein expression in the monocytes and vasculature is important for elevated blood pressure. Increased rhythmicity in hypertensive arterial smooth muscle was also found to be related to TRPCs [62]. Another study found that norepinephrine-induced vasomotion and Ca^{2+} influx were increased in mesenteric arterioles from SHRs, consistent with up-regulated expression of TRPC1, TRPC3 and TRPC5 [62]. TRPC6 knockout mice have shown greatly enhanced expression of TRPC3 and enhanced agonist-induced arterial vasoconstriction, consequently exhibiting increased blood pressure [40]. This find-

ing suggested that increased TRPC3 expression relative to that of TRPC6 may predispose mice to hypertension [63]. The expression level of TRPC6 and the Ca^{2+} influx currents it mediated have been found to be increased in the mesenteric arteries of deoxycorticosterone acetate-salt hypertensive rats [64]. These studies suggest that dysfunction of TRP channel subtype C contributes to altered vascular reactivity and promotes the development of hypertension.

5 TRP channel subtypes M and V have anti-hypertensive effects

Some TRP channels contribute to vasodilatation and may attenuate hypertension. Intracellular magnesium depletion has been implicated in the vascular dysfunction of hypertension. Considering that TRPM7 is Mg^{2+}-permeant channel responsible for transcellular Mg^{2+} transport. Altered cellular Mg^{2+} homeostasis and abnormal VSMC function in hypertension may be related to defective TRPM7 expression/activity [65,66]. Touyz et al. [67] demonstrated that TRPM7 was present and functionally active in human, mouse and rat VSMCs. Furthermore, they found that TRPM6 was unaltered in SHR, but expression of TRPM7 was blunted. This was associated with attenuated annexin-1 translocation and decreased VSMC $[Mg^{2+}]i$ in SHR [68]. TRPM8 is involved in the regulation of vascular tone, and the down-regulation of TRPM8 may contribute to enhanced vasoreactivity in pulmonary hypertension [69]. TRPM8 activation by menthol was found to attenuate vasoconstriction via RhoA/ROCK pathway inhibition [56]. Chronic dietary menthol blunted mesenteric arterial constriction and lowered blood pressure in both SHRs and pre-hypertensive individuals [56]. Flow-mediated dilatation in pre-hyperten- sive individuals was also improved by chronic menthol administration [56]. Growing evidence suggests that TRPV1 channels play multiple important roles in hypertension via several different mechanisms. TRPV1 activation exerts anti-hypertension effects by stimulating the release of calcitonin gene-related peptide (CGRP) from capsaicin-sensitive sensory nerves and NO from ECs [26,70]. *In vivo*, plasma concentration of CGRP rises transiently after acute administration of capsaicin in adult rats, accompanied by a decrease in blood pressure [71]. In a previous study, we showed that the TRPV1 agonist capsaicin acutely relaxed mesenteric arteries through at least two mechanisms: a direct action on ECs, which was NO dependent and L-NAME sensitive, and the release of CGRP, which activated an L-NAME-insensitive pathway, but to a lesser degree [26]. Activation of TRPV1 enhanced endothelium-dependent relaxation in wild-type mice, an effect absent in TRPV1- deficient mice [26]. In another study, long-term stimulation of TRPV1 by dietary capsaicin attenuated hypertension in SHRs [26]. TRPV1 channels have also been proposed to be involved in the pathogenesis of salt-induced hypertension. TRPV1 expression in mesenteric resistance arteries, the renal cortex and medulla, CGRP levels in dorsal root ganglia, and CGRP-positive sensory nerve density in mesenteric resistance arteries were significantly up-regulated during

Table 1 TRP channels in vascular function regulation and hypertension

TRP channels	Distribution	Proposed roles	Main references
TRPC1	VSMC	A component of store-operated Ca^{2+} entry pathway, contributing to enhanced vasoconstriction.	[33–35]
TRPC1/TRPC3	VSMC	1. Inhibited by the NO/cGMP/PKG pathway, contributes to NO-induced vasodilatation. 2. Increased expression and contribution to increased vasomotion in hypertension	[51] [62]
TRPC3	VSMC EC	1. Involved in UTP-mediated depolarization and vasoconstriction. 2. Facilitates endothelium-derived hyperpolarization-mediated resistance artery vasodilatation.	[37] [52,53]
TRPC3, TRPC5	VSMC monocyte	Increased expression and Ca^{2+} influx in VSMC and monocytes from hypertensive animals and patients.	[1,60–62]
TRPC4	EC	Functions as Ca^{2+} conducting, non-selective cation channel and contributes to vasodilatation	[54]
TRPC5	VSMC	Activation of TRPC5 by sphingosine-1-phospate, controlling VSMC motility.	[38]
TRPC6	VSMC	1. Regulation of myogenic tone. 2. TRPC6-deficient mice show elevated blood pressure and enhanced vasoconstriction. 3. Implicated in deoxycorticosterone acetate-salt-induced hypertension.	[39] [40] [64]
TRPV1	EC	1. Involved in endothelium-dependent vasodilatation. 2. TRPV1 activation prevents hypertension. 3. Related to salt-induced increase in blood pressure. 4. Regulation of salt-intake behaviors that are associated with salt-sensitive hypertension.	[26,70–74]
TRPV2	VSMC	Implicated in mechano-sensitive membrane depolarization and hypotonic stimulation	[48]
TRPV4	VSMC, EC	1. TRPV4 activation in the EC and VSMC promotes vasodilatation. 2. Enhanced TRPV4 expression may counterbalance salt-induced increases in blood pressure.	[28,55] [75]
TRPM4	VSMC	Contribution to pressure-induced vasoconstriction and control of cerebral artery myogenic tone.	[45,46]
TRPM7	VSMC	Defective TRPM7 expression/activity contribute to altered cellular Mg^{2+} homeostasis and abnormal VSMC function in SHRs.	[65–68]
TRPM8	VSMC	1. Attenuates vasoconstriction via RhoA/ROCK pathway and lowers blood pressure. 2. Reduced TRPM8 may contribute to the enhanced vasoreactivity in PH.	[56] [69]
TRPA1	EC	Mediates vasodilatation via endothelium-dependent and independent mechanisms.	[57,58]
TRPP2	VSMC	Contributes to the myogenic response of resistance-size cerebral arteries	[47]

high-salt intake in Dahl salt-resistant rats, which acted to prevent salt-induced increases in blood pressure [72]. In contrast, TRPV1 expression and function was impaired in Dahl salt-sensitive rats, which rendered Dahl salt-sensitive rats to salt load in terms of blood pressure regulation [72]. Hao et al. [73] showed that endothelium-dependent relaxation in mesenteric resistance arteries was impaired in mice fed on high-salt diet, which was associated with increased superoxide anion generation and reduced NO levels. Activation of TRPV1 by dietary capsaicin was found to reduce the high-salt-intake induced endothelial dysfunction, and nocturnal hypertension, in part by preventing the vascular oxidative stress [73]. TRPV1 may also mediate a general aversive response to salt, indicating a role for TRPV1 in regulating salt intake behaviors, which are tightly related to the development of salt-sensitive hypertension [74]. TRPV4 channels are also critically associated with salt-sensitive hypertension. High-salt intake may up-regulate the expressio n and function of TRPV4 to counterbalance salt-induced increases in blood pressure in a salt-resistant strain of rats [75]. WNK4 is a member of WNK kinase family and regulates the expression of TRPV4. Functional regulation of TRPV4 by WNK4 may influence systemic Ca^{2+} balance and contribute to vascular function and blood pressure regulation. Mutations in the gene encoding WNK4 have been linked to monogenic hypertension [76]. These findings highlight a promising role for TRP channel subtype M and V in the treatment of hypertension.

Functional equilibrium between different TRP channels subtypes plays a critical role in maintaining vascular physiological function and normal blood pressure. If this delicate balance is broken, it may cause vascular dysfunction and lead to high blood pressure. This hypothesis was supported by our previous study, which revealed enhanced TRPC3/5 mediated vasoconstriction and impaired TRPV1/TRPM8-induced vasodilatation in hypertension [4,26,56,62,77], in parallel with similar findings from other groups. Thus, we propose an imbalance of TRP channel functions as a new etiology for hypertension (Figure 1).

6 Perspectives and conclusion

Elucidating the roles of TRP channels, acting both singly and as a network, in the physiology and pathology of vascular function and blood pressure regulation is of prime importance. To achieve this goal, new strategies, including systems biology, engineering of novel animal models related to TRP channels, optic-genetics and channelomics, may be helpful. Currently, the lack of specific TRP channel subtype C modulators restricts their application in the management of hypertension. There is an urgent need for novel modulators of TRP channels. Furthermore, translational research on TRP channels should be accelerated. New research findings should be taken from the bench to the bedside. In conclusion, TRP channels exert multiple functions

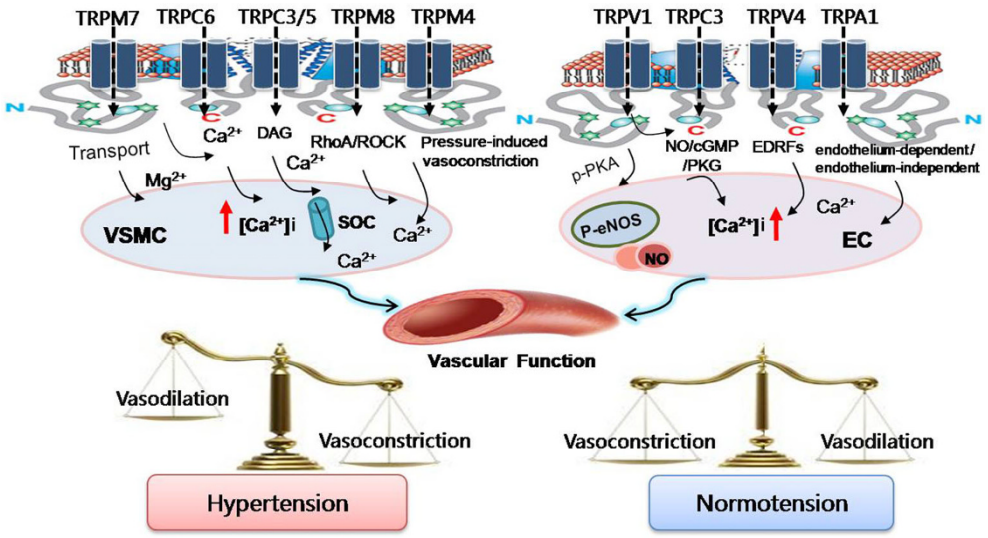

Figure 1 (color online) Functional balance of TRP channels in the regulation of vascular function and blood pressure. Based on their role in vasculature function regulation, TRP channels can be divided into two functional subtypes: one that participates in vasoconstriction and one that participates in vasodilatation. Activation of TRPC3/5 expression results in an increase in VSMC $[Ca^{2+}]i$ via SOC- and DAG-mediated Ca^{2+} influx. Ang II and norepinephrine up-regulate TRPC3/5 expression and lead to Ca^{2+} influx and vasoconstriction as well as increased blood pressure. TRPC6-deficient mice show elevated blood pressure and enhanced vasoconstriction. TRPM4 is associated with pressure-induced vasoconstriction. Reduced expression of TRPM7 contributes to vasoconstriction in SHRs. Activation of TRPM8 by menthol inhibits Ca^{2+} signaling-mediated RhoA/ROCK activation in the vasculature and lowers blood pressure. TRPV4 is involved in temperature dependent and shear stress-induced vasodilatation in the EC. TRPC3 facilitates endothelium-derived hyperpolarization-mediated resistance artery vasodilatation. TRPA1 via endothelium-dependent and independent contributes to vasodilatation. Activation of TRPV1 by capsaicin increases the pPKA and eNOS in ECs, thereby leading to enhanced vasodilatation and lower blood pressure.

in the physiological regulation of vascular function and blood pressure. An imbalance in TRP channels' multiple functions may impair vascular function and lead to high blood pressure.

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